Advances in Clinical Medicine 临床医学进展, 2024, 14(2), 4227-4233
Published Online February 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.142585

Hans汉斯

高原肺水肿中的炎症与巨噬细胞免疫作用

李佳文[1*]，鲍海华[2#]

[1]青海大学附属医院影像中心，青海 西宁
[2]青海大学研究生院，青海 西宁

收稿日期：2024年1月29日；录用日期：2024年2月23日；发布日期：2024年2月29日

摘 要

高原肺水肿(High Altitude Pulmonary Edema, HAPE)是机体对低氧环境不同程度适应性导致肺液稳态调节不平衡而引起的高原危重症。目前已有的发生机制主要为血流动力学、渗液机制、肺水清除障碍、炎症反应等。缺氧诱导的炎症机制参与了HAPE，肺泡和肺血管壁中最突出的炎症细胞类型是巨噬细胞。本研究拟通过综述类形式从炎症与巨噬细胞免疫作用角度谈HAPE的发病机制及研究进展，以期对HAPE的研究及临床预防和(或)治疗具有一定推动作用。

关键词

肺巨噬细胞，炎症，HIF，高原肺水肿

Inflammation and Macrophage Immunity in High Altitude Pulmonary Edema

Jiawen Li[1*], Haihua Bao[2#]

[1]Imaging Center of Qinghai University Affiliated Hospital, Xining Qinghai
[2]Postgraduate School of Qinghai University, Xining Qinghai

Received: Jan. 29th, 2024; accepted: Feb. 23rd, 2024; published: Feb. 29th, 2024

Abstract

High Altitude Pulmonary Edema (HAPE) is a critical illness caused by imbalance of lung fluid homeostasis regulation due to different degrees of adaptation to low oxygen environment. Currently, the main mechanisms of HAPE are hemodynamics, exudate mechanism, impaired lung water clear-

*第一作者。
#通讯作者。

文章引用: 李佳文, 鲍海华. 高原肺水肿中的炎症与巨噬细胞免疫作用[J]. 临床医学进展, 2024, 14(2): 4227-4233.
DOI: 10.12677/acm.2024.142585

ance, and inflammatory response. Hypoxia-induced inflammatory mechanisms are involved in HAPE, and the most prominent inflammatory cell type in the alveolar and pulmonary vascular walls are macrophages. This study intends to discuss the pathogenesis and research progress of HAPE from the perspective of inflammation and macrophage immune action in the form of a review class, in order to have a promotion effect on the research and clinical prevention and/or treatment of HAPE.

Keywords

Pulmonary Macrophage, Inflammation, HIF, High Altitude Pulmonary Edema

1. 引言

高原肺水肿(High altitude pulmonary edema, HAPE)多发生于初次或再次急进海拔 > 2500 m 地区的人群，是机体对低氧环境不同程度适应性导致肺液稳态调节不平衡而引起的高原危重症。目前对于高原肺水肿的发病机制尚不清楚，已有的发病机制包括：血流动力学、渗液机制、炎症反应、肺泡清除能力下降、氧化应激、遗传因素等[1]。本研究拟通过综述类形式从炎症与巨噬细胞免疫作用角度谈 HAPE 的发病机制及研究进展，以期对 HAPE 的研究及临床预防和(或)治疗具有一定推动作用。

2. 在 HAPE 中存在炎症浸润的证据

缺氧和炎症之间的相互作用已经在包括肺动脉高压在内的一系列疾病中得到了广泛的记录[2]。严重缺氧条件下，通常低于 3%的 O_2，会导致血管内皮细胞和循环髓系细胞释放促炎细胞因子。细胞因子释放的缺氧刺激是相当迅速的，且发生在数小时内，因此可能是 HAPE 的早期事件[3]。支持人体肺部在缺氧状态下存在炎症，有学者对对至少持续 1-2 天的 HAPE 患者进行两项不同的肺泡灌洗研究并通过支气管镜收集的肺泡液，发现相当高的 IL-1β、IL-6、IL-8、TNF-α 和 IL-Rra，以及中性粒细胞浸润[4] [5]。越来越多的证据表明，缺氧改变了肺非血管细胞中各种血管活性和炎症因子的表达，如巨噬细胞、淋巴细胞和树突状细胞[6]。研究发现不同时间(2~28 d)模拟高原低氧均可诱导小鼠肺组织中内皮细胞中 CAMs 基因的转录激活，增强免疫细胞和血管上皮细胞的炎症反应，肺部渗出液增多而促进 HAPE 发生[7]。在高海拔环境中还未发生 HAPE 的登山者 IL-1、IL-6、TNF-α 等炎症标志物水平升高。呼吸道感染细菌、病毒及其毒素、炎性代谢产物等均可直接损害肺组织毛细血管，使其通透性增高，在高原低氧状况下这种损害更显剧烈[8]。另有研究发现[9]，肺肥大细胞(Mast cells, MCs)在急性低氧条件下快速发生募集，在肺微小血管旁快速增多、活性增强，脱颗粒释放 IL-6 增多，与类胰蛋白酶参与了肺 MC 活化的瀑布效应，直接或间接释放缩血管物质增多，参与促进了低氧 PAP 增高的过程，进一步促进 HAPE 的发生。此外，最近的一项研究表明，炎症相关基因(MMP8、MMP9、IL-17β 和 Timp1)的表达在暴露于相同缺氧条件(急性低压缺氧)的大鼠肺部上调[10]。综上认为缺氧诱发的肺部和/或全身炎症可能是 HAPE 的一个病因。

3. 在 HAPE 中肺巨噬细胞的时空特异性激活

在缺氧 PH 小鼠模型中，在不同时间点从肺泡和间质/血管周围腔室分离巨噬细胞为，间质巨噬细胞

(interstitial macrophages, IMs)，将他们称为 CD11bhi 巨噬细胞。肺泡巨噬细胞(alveolar macrophage, AMs)，将他们称为 CD11chi 巨噬细胞。AMs 由一个单一的驻留细胞群组成，这些细胞在整个缺氧过程中在数量上保持稳定，没有巨噬细胞募集到肺泡腔室。IMs 由基线时的单一驻留细胞群，缺氧 4 天后的驻留细胞和招募细胞混合群，以及缺氧 14 天后更同质的重编程巨噬细胞群组成。缺氧早期，肺泡和间质室的肺巨噬细胞显示出保守的“缺氧程序”，其特征是细胞代谢的变化，包括氧化磷酸化、线粒体功能障碍和糖酵解，EIF2、RhoA、肌动蛋白细胞和 mTORC1 信号通路的增加致促炎基因激活和代谢的改变，而后来在缺氧过程中，AMs 继续保持这种激活状态，IMs 存在编程向表达抗炎和促修复基因和通路的独特表型转移，这种编程变化伴随着血管周围巨噬细胞数量的显著减少[11]。由此可见，缺氧导致巨噬细胞向间质/血管周围空间的早期积累[12]。研究挑战了目前的一个假设，即肺泡巨噬细胞数量的增加是由于循环细胞的募集[12] [13]。

急性低氧应激可刺激肺血管发生低氧性肺血管收缩(hypoxic pulmonary vasoconstriction, HPV)，是血流从低氧肺泡区转移到通气较好的肺泡区，发生肺内血流重新分配，使肺部整体的通气/血流比值维持在最佳比值，以保证肺换气的完成，维持较高的血氧分压[14]。缺氧导致肺泡炎症，主要由巨噬细胞组成。IMs 容易被招募到低氧张力下血管供应不足的区域[15]。被招募的巨噬细胞可以通过极化激活来适应其免疫微环境，大致可以分为两种类型：经典型巨噬细胞(M1)和替代性活化巨噬细胞(M2)和抗炎(调节)巨噬细胞[16] [17] [18]。M1 是“效应”吞噬细胞，由干扰素-γ (INF-γ)和肿瘤坏死因子(TNF-α)激活。它们产生诱导型一氧化氮合酶(iNOS)和 IL-12，通过鼓励促炎分子的释放，增强了炎症反应，并表现出增强的杀微生物或杀瘤能力[16]。M2 通过其促进营养、促纤维化、刺激细胞增殖和血管生成，参与了肺和其他疾病的发病机制[19] [20]。研究首次检测小鼠 HPH 发育过程中 M1 和 M2 巨噬细胞比例的动态变化。作者发现 M1 巨噬细胞浸润在炎症急性期(始于缺氧第 4 天)占主导地位，随后向抗炎 M2 表型的转变可能会过度的组织损伤[21]。另有研究发现体内和体外的缺氧使肺泡巨噬细胞的数量向 M2 表型极化。初级肺泡在缺氧条件下体外培养的巨噬细胞(0.5% O_2)也表现出 M2 表型，Fizz1 和 Ym1 水平增加，而不是 IL-12 和 TNF-α，表明缺氧诱导的 M2 极化是一种细胞自主现象[22]。在体内，最近发现的两种 M2 极化的非典型诱导剂 CCL2 和 IL-6 的 mRNA 水平的上调[23]，以及缺氧小鼠 BALF 中 IL-13 和 IL-4 细胞因子水平的升高，支持了我们的缺氧模型中的 M2 样激活[24]。

4. 在 HAPE 中肺巨噬细胞与炎症级联反应

缺氧诱导 AMs 释放单核细胞趋化转录蛋白-1 (MCP-1) [25]，一种具有肥大细胞促分泌特性的趋化因子，该介质被循环转移并激活肥大细胞，活化的 MCs 导致微血管炎症，其中白细胞－内皮细胞粘附相互作用增加，白细胞迁移和血管通透性增加[26]。局部肾素-血管紧张素系统(RAS)被肥大细胞脱颗粒激活，参与炎症级联反应，Ang I 的缩血管作用很微弱，ACE 在肺毛细血管内皮细胞上活性表达最高，但当其进入到肺循环后会在 ACE 的作用下转变为具有强烈收缩血管作用的活性物质 Ang II，肺循环是体内唯一不使 Ang II 灭活的血管床，Ang II 是重要的血管损伤因子，能引起内皮细胞肿胀、呈上皮细胞凋亡。研究发现 Ang II 可激发炎症反应及细胞氧化应激，诱导肺组织损伤[27]。由于全身炎症仅发生在肺泡 PO_2 减少时，肺泡巨噬细胞由于其位置和全身作用，被认为可能是肺泡缺氧全身炎症的循环介质的来源。AMs 在这一现象中的作用被三条证据证明[28]：首先，通过气管灌注含氯膦酸脂质体消耗 AMs 阻断肥大细胞脱颗粒、白细胞－内皮细胞粘附增加和肺泡缺氧后白蛋白外渗。第二，从缺氧、AMs 衰竭的大鼠获得的血浆应用于正常氧嵴时没有引起炎症；第三，AMs 原代培养上清液暴露于 10% O_2 诱导肥大细胞脱颗粒和白细胞内皮粘附，观察常氧培养的肺泡巨噬细胞上清液无炎症作用，排除了非特异性效应。总之，强有力的证据支持关于 AMs 激活的系统性影响。

5. 在 HAPE 中肺巨噬细胞与肺循环结构重构

缺氧状态下血流动力学的改变会导致肺内皮细胞(Epithelial Cells, ECs)功能障碍，表现为增加其通透性和炎症细胞标记物的表达，并干扰多种细胞质膜依赖的受体、代谢和转运功能，进而导致免疫细胞的粘附和炎症介质的释放，而由此产生的血管周围炎症[29] [30]。越来越多的证据，已经证明外膜的变化是血管壁炎症性病变发展的直接驱动力[31]-[36]。在 ECs 损伤时，外膜除成纤维细胞本身表现出促炎表型(包括外膜巨噬细胞的募集、激活和促炎标志物的产生)外，还包含白细胞、祖细胞、神经(交感神经和副交感神经)、淋巴管和血管(额外的血液供应)，这些已被证明在 ECs 损伤时被集体激活，并释放多种因子，驱动先天免疫细胞的募集[37] [38] [39] [40] [41]。炎细胞如活化的巨噬细胞分泌 MMPs，特别是 MMP-2 [42] [43]、MMP-9 [43] [44]、MMP-10 [45]和 MMP-19 [42] [44]，而金属蛋白酶组织抑制剂(TIMPs)出现下调[37] [43]。MMPs，降解弹性蛋白，促进外膜成纤维细胞和其转化来的肌成纤维细胞向中膜和内膜的迁移[37] [42]，促进平滑肌细胞(Smooth Muscle Cells, SMCs)从中膜迁移到动脉壁内膜区域形成新生内膜[46] [47]。被招募 IMs 可能表达细胞外基质(ExtraCellularr Matrix, ECM)蛋白，如 I 型胶原[48]。炎症介质刺激成纤维细胞[42]可增加胶原蛋白[49]、纤维连接蛋白或基质细胞 tenascin-C 的表达[50]。最终，血管壁弹性蛋白纤维成分逐渐不平衡，ECM 重构，降低血管顺应性。

肺血管床的 ECs 可以感知到由血管顺应性降低引起的压力升高和高搏动血流，触发炎症细胞因子 IL-6 和 TNF，趋化因子(C-C motif)配体 2 (CCL2)、基质金属蛋白酶(MMP)-9、血小板衍生生长因子 B 和白三烯 B4 (LTB4)，并表达水平升高的免疫细胞粘附分子，包括血管细胞粘附分子 1 (VCAM-1)、细胞间粘附分子 1 (ICAM-1)和 P-选择素[51] [52]，这些已知炎症介质的积累可能产生促炎微环境，不利于肺血管床的完整性，从而进一步恶化血管重构，从肺泡毛细血管屏障压力梯度及通透性和淋巴通量的动态变化到流体静力平衡的破坏所有这些元素都有助于血管外肺水的增加[3]。

6. 在 HAPE 中肺巨噬细胞与 HIF 信号的相互作用

缺氧驱动免疫/炎症介导复杂的血管稳态，转录反应的关键调控因子分别是缺氧诱导因子(Hypoxia inducible factor, HIF)和核因子-κB (NF-κB) [53]。缺氧通过 TNF-α/NF-kB/HIF 信号级联通路与免疫细胞的代谢重构和炎症控制相互作用。Jin [54]等人发现，在应对缺氧时，内皮细胞可以有效分泌 TNF-α，进而通过 NF-κB 通路激活 HIF。一方面，HIF 通过与 NF-κB 信号通路的串扰驱动细胞因子的释放，这增强了巨噬细胞的募集、趋化性和极化性(促进免疫细胞的激活、代谢重编程和炎症介质的释放)。另一方面，暴露于缺氧环境中的免疫细胞，会激活和稳定 HIF。在缺氧条件下，抑制线粒体氧化磷酸化和电子传递链被抑制，而糖酵解被增强，导致巨噬细胞活性氧(ROS)和琥珀酸和富马酸等代谢物的产生增加，从而激活和稳定 HIF-1α [55]。HIF-1α 还通过抑制细胞凋亡和触发核因子 NF-κB 信号通路来增加中性粒细胞胞外陷阱(NETs)的形成和中性粒细胞的存活。活化的中性粒细胞刺激 HIF-1α 和 HIF-2α 的表达[56] [57]。因此，HIF 介导的免疫细胞失调和 HIF/NF-κB 串扰共同参与了 HAPE 的病理。

7. 结论

综上所述，缺氧诱导的炎症机制参与了 HAPE。肺巨噬细胞向保守的缺氧程序的早期腔室独立激活，与 TNF-α/NF-κB/HIF 信号级联通路串扰促进微循环炎症反应，直接或通过血管壁其他成分间接参与肺循环结构重构，在不同水平的炎症级联的体循环中发挥重要作用，共同参与了 HAPE 的病理。因此，肺巨噬细胞在缺氧诱导的肺损伤中观察到的炎症反应中具有突出的作用。但可以肯定的是，肺巨噬细胞与 HAPE 之间的联系远不止目前这些，其分子机制有待进一步去探索，以期未来为更多系统疾病提供新的参考。由于高原地区的特殊性，该方面疾病研究相对偏少，以期学者们未来更多领域、更深层次的探讨。

参考文献

[1] 付兴, 付义. 高原肺水肿发病机制及中医药防治研究进展[J]. 中国中医基础医学杂志, 2019, 25(4): 563-566.

[2] Pugliese, S.C., Poth, J.M., Fini, M.A., Olschewski, A., El Kasmi, K.C. and Stenmark, K.R. (2015) The Role of Inflammation in Hypoxic Pulmonary Hypertension: From Cellular Mechanisms to Clinical Phenotypes. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, **308**, L229-L252. https://doi.org/10.1152/ajplung.00238.2014

[3] Swenson, E.R. (2020) Early Hours in the Development of High-Altitude Pulmonary Edema: Time Course and Mechanisms. *Journal of Applied Physiology*, **128**, 1539-1546. https://doi.org/10.1152/japplphysiol.00824.2019

[4] Kubo, K., Hanaoka, M., Hayano, T., Miyahara, T., Hachiya, T., Hayasaka, M., *et al.* (1998) Inflammatory Cytokines in BAL Fluid and Pulmonary Hemodynamics in High-Altitude Pulmonary Edema. *Respiration Physiology*, **111**, 301-310. https://doi.org/10.1016/S0034-5687(98)00006-1

[5] Schoene, R.B., Swenson, E.R., Pizzo, C.J., Hackett, P.H., Roach, R.C., Mills Jr., *et al.* (1988) The Lung at High Altitude: Bronchoalveolar Lavage in Acute Mountain Sickness and Pulmonary Edema. *Journal of Applied Physiology*, **64**, 2605-2613. https://doi.org/10.1152/jappl.1988.64.6.2605

[6] Stenmark, K.R., Davie, N.J., Reeves, J.T. and Frid, M.G. (2005) Hypoxia, Leukocytes, and the Pulmonary Circulation. *Journal of Applied Physiology*, **98**, 715-721. https://doi.org/10.1152/japplphysiol.00840.2004

[7] 高钰琪, 高文祥, 袁志兵, 等. 低氧肺血管炎症反应是高原肺水肿和低氧性肺动脉高压形成的关键环节[J]. 中国病理生理杂志, 2015, 31(10): 1903.

[8] Li, Y., Zhang, Y. and Zhang, Y. (2018) Research Advance in Pathogenesis and Prophylactic Measures of Acute High Altitude Illness. *Respiratory Medicine*, **145**, 145-152. https://doi.org/10.1016/j.rmed.2018.11.004

[9] 刘杰, 曹成珠, 纪巧荣, 等. 不同急性低氧条件下 SD 大鼠肺肥大细胞的变化趋势[J]. 中国高原医学与生物学杂志, 2020, 41(1): 24-32.

[10] Fu, X., Yang, C., Chen, B., Zeng, K., Chen, S. and Fu, Y. (2021) Qi-Long-Tian Formula Extract Alleviates Symptoms of Acute High-Altitude Diseases via Suppressing the Inflammation Responses in Rat. *Respiratory Research*, **22**, Article No. 52. https://doi.org/10.1186/s12931-021-01645-8

[11] Pugliese, S.C., Kumar, S., Janssen, W.J., Graham, B.B., Frid, M.G., Riddle, S.R., *et al.* (2017) A Time- and Compartment-Specific Activation of Lung Macrophages in Hypoxic Pulmonary Hypertension. *The Journal of Immunology*, **198**, 4802-4812. https://doi.org/10.4049/jimmunol.1601692

[12] Frid, M.G., Brunetti, J.A., Burke, D.L., Carpenter, T.C., Davie, N.J., Reeves, J.T., *et al.* (2006) Hypoxia-Induced Pulmonary Vascular Remodeling Requires Recruitment of Circulating Mesenchymal Precursors of a Monocyte/Macrophage Lineage. *The American Journal of Pathology*, **168**, 659-669. https://doi.org/10.2353/ajpath.2006.050599

[13] Ensan, S., Li, A., Besla, R., Degousee, N., Cosme, J., Roufaiel, M., *et al.* (2016) Self-Renewing Resident Arterial Macrophages Arise from Embryonic CX3CR1^{+} Precursors and Circulating Monocytes Immediately after Birth. *Nature Immunology*, **17**, 159-168. https://doi.org/10.1038/ni.3343

[14] 范勇, 史玉玲, 刘杰. 高原肺水肿发病机制及防治研究进展[J]. 河南中医, 2023, 43(9): 1435-1444.

[15] Lewis, C. and Murdoch, C. (2005) Macrophage Responses to Hypoxia: Implications for Tumor Progression and Anti-Cancer Therapies. *The American Journal of Pathology*, **167**, 627-635. https://doi.org/10.1016/S0002-9440(10)62038-X

[16] Mosser, D.M. and Edwards, J.P. (2008) Exploring the Full Spectrum of Macrophage Activation. *Nature Reviews Immunology*, **8**, 958-969. https://doi.org/10.1038/nri2448

[17] Edwards, J.P., Zhang, X., Frauwirth, K.A. and Mosser, D.M. (2006) Biochemical and Functional Characterization of Three Activated Macrophage Populations. *Journal of Leukocyte Biology*, **80**, 1298-1307. https://doi.org/10.1189/jlb.0406249

[18] Murray, P.J., Allen, J.E., Biswas, S.K., Fisher, E.A., Gilroy, D.W. and Goerdt, S. (2014) Macrophage Activation and Polarization: Nomenclature and Experimental Guidelines. *Immunity*, **41**, 14-20. https://doi.org/10.1016/j.immuni.2014.06.008

[19] Mora, A.L., Torres-Gonzalez, E., Rojas, M., Corredor, C., Ritzenthaler, J., Xu, J., *et al.* (2006) Activation of Alveolar Macrophages via the Alternative Pathway in Herpesvirus Induced Lung Fibrosis. *American Journal of Respiratory Cell and Molecular Biology*, **35**, 466-473. https://doi.org/10.1165/rcmb.2006-0121OC

[20] Shaykhiev, R., Krause, A., Salit, J., Strulovici-Barel, Y., Harvey, B.G., O'Connor, T.P. and Crystal, R.G. (2009) Smoking-Dependent Reprogramming of Alveolar Macrophage Polarization: Implication for Pathogenesis of Chronic Obstructive Pulmonary Disease. *The Journal of Immunology*, **183**, 2867-2883. https://doi.org/10.4049/jimmunol.0900473

[21] Liu, H., Wang, Y., Zhang, Q., Liu, C., Ma, Y., Huang, P., Ge, R. and Ma, L. (2023) Macrophage-Derived Inflammation Promotes Pulmonary Vascular Remodeling in Hypoxia-Induced Pulmonary Arterial Hypertension Mice. Immunol Lett, **263**, 113-122. https://doi.org/10.1016/j.imlet.2023.10.005

[22] Vergadi, E., Chang, M.S., Lee, C., Liang, O.D., Liu, X., Fernandez-Gonzalez, A., *et al.* (2011) Early Macrophage Recruitment and Alternative Activation Are Critical for the Later Development of Hypoxia-Induced Pulmonary Hypertension. *Circulation*, **123**, 1986-1995. https://doi.org/10.1161/CIRCULATIONAHA.110.978627

[23] Roca, H., Varsos, Z.S., Sud, S., Craig, M.J., Ying, C. and Pienta, K.J. (2009) CCL2 and IL-6 Promote Survival of Human $CD11b^+$ Peripheral Blood Mononuclear Cells and Induce M2-Type Macrophage Polarization. *Journal of Biological Chemistry*, **284**, 34342-34354. https://doi.org/10.1074/jbc.M109.042671

[24] Teng, X., Li, D., Champion, H.C. and Johns, R.A. (2003) FIZZ1/RELMα, a Novel Hypoxia-Induced Mitogenic Factor in Lung with Vasoconstrictive and Angiogenic Properties. *Circulation Research*, **92**, 1065-1067. https://doi.org/10.1161/01.RES.0000073999.07698.33

[25] Chao, J., Donham, P., Van Rooijen, N., Wood, J.G. and Gonzalez, N.C. (2011) Monocyte Chemoattractant Protein-1 Released from Alveolar Macrophages Mediates the Systemic Inflammation of Acute Alveolar Hypoxia. *American Journal of Respiratory Cell and Molecular Biology*, **45**, 53-61. https://doi.org/10.1165/rcmb.2010-0264OC

[26] Chao, J., Wood, J.G. and Gonzalez, N.C. (2009) Alveolar Hypoxia, Alveolar Macrophages, and Systemic Inflammation. *Respiratory Research*, **10**, Article No. 54. https://doi.org/10.1186/1465-9921-10-54

[27] 麻海英, 洒玉萍, 沈慧萍, 等. 血管紧张素转化酶、血管紧张素Ⅱ在高原肺水肿中的相关研究进展[J]. 吉林医学, 2021, 42(3): 741-743.

[28] Gonzalez, N.C., Allen, J., Blanco, V.G., Schmidt, E.J., Van Rooijen, N. and Wood, J.G. (2007) Alveolar Macrophages Are Necessary for the Systemic Inflammation of Acute Alveolar Hypoxia. *Journal of Applied Physiology*, **103**, 1386-1394. https://doi.org/10.1152/japplphysiol.00312.2007

[29] Ye, Y., Xu, Q. and Wuren, T. (2023) Inflammation and Immunity in the Pathogenesis of Hypoxic Pulmonary Hypertension. *Frontiers in Immunology*, **14**, Article 1162556. https://doi.org/10.3389/fimmu.2023.1162556

[30] Richalet, J.P., Jeny, F., Callard, P. and Bernaudin, J.F. (2023) High-Altitude Pulmonary Edema: the Intercellular Network Hypothesis. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, **325**, L155-L173. https://doi.org/10.1152/ajplung.00292.2022

[31] Spiekerkoetter, E., Goncharova, E.A., Guignabert, C., Stenmark, K., Kwapiszewska, G. and Rabinovitch, M. (2019) Hot Topics in the Mechanisms of Pulmonary Arterial Hypertension Disease: Cancer-Like Pathobiology, the Role of the Adventitia, Systemic Involvement, and Right Ventricular Failure. *Pulmonary Circulation*, **9**, 1-15. https://doi.org/10.1177/2045894019889775

[32] Buckley, C.D., Barone, F. and Nayar, S. (2015) Stromal Cells in Chronic Inflammation and Tertiary Lymphoid Organ Formation. *Annual Review of Immunology*, **33**, 715-745. https://doi.org/10.1146/annurev-immunol-032713-120252

[33] Libby, P. (2015) Fanning the Flames: Inflammation in Cardiovascular Diseases. *Cardiovascular Research*, **107**, 307-309. https://doi.org/10.1093/cvr/cvv188

[34] Libby, P. and Hansson, G.K. (2015) Inflammation and Immunity in Diseases of the Arterial Tree: Players and Layers. *Circulation Research*, **116**, 307-311. https://doi.org/10.1161/CIRCRESAHA.116.301313

[35] Maiellaro, K. and Taylor, W.R. (2007) The Role of the Adventitia in Vascular Inflammation. *Cardiovascular Research*, **75**, 640-648. https://doi.org/10.1016/j.cardiores.2007.06.023

[36] Wang, J., Wang, Y. and Wang, J. (2018) Adventitial Activation in the Pathogenesis of Injury-Induced Arterial Remodeling: Potential Implications in Transplant Vasculopathy. *The American Journal of Pathology*, **188**, 838-845. https://doi.org/10.1016/j.ajpath.2017.12.002

[37] Stenmark, K.R., Yeager, M.E. and El Kasmi, K.C. (2013) The Adventitia: Essential Regulator of Vascular Wall Structure and Function. *Annual Review of Physiology*, **75**, 23-47. https://doi.org/10.1146/annurev-physiol-030212-183802

[38] Majesky, M.W., Dong, X.R. and Hoglund, V. (2011) The Adventitia: A Dynamic Interface Containing Resident Progenitor Cells. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **31**, 1530-1539. https://doi.org/10.1161/ATVBAHA.110.221549

[39] El Kasmi, K.C., Pugliese, S.C., Riddle, S.R., Poth, J.M., Anderson, A.L. and Frid, M.G. (2014) Adventitial Fibroblasts Induce a Distinct Proinflammatory/Profibrotic Macrophage Phenotype in Pulmonary Hypertension. *The Journal of Immunology*, **193**, 597-609. https://doi.org/10.4049/jimmunol.1303048

[40] Kuebler, W.M., Bonnet, S. and Tabuchi, A. (2018) Inflammation and Autoimmunity in Pulmonary Hypertension: Is There a Role for Endothelial Adhesion Molecules? (2017 Grover Conference Series). *Pulmonary Circulation*, **8**, 1-13. https://doi.org/10.1177/2045893218757596

[41] Hu, Y., Chi, L., Kuebler, W.M. and Goldenberg, N.M. (2020) Perivascular Inflammation in Pulmonary Arterial

Hypertension. *Cells*, **9**, Article 2338. https://doi.org/10.3390/cells9112338

[42] Sun, W. and Chan, S.Y. (2018) Pulmonary Arterial Stiffness: An Early and Pervasive Driver of Pulmonary Arterial Hypertension. *Frontiers in Medicine* (*Lausanne*), **5**, Article 204. https://doi.org/10.3389/fmed.2018.00204

[43] Lammers, S., Scott, D., Hunter, K., Tan, W., Shandas, R. and Stenmark, K.R. (2012) Mechanics and Function of the Pulmonary Vasculature: Implications for Pulmonary Vascular Disease and Right Ventricular Function. *Comprehensive Physiology*, **2**, 295-319. https://doi.org/10.1002/cphy.c100070

[44] Savai, R., Pullamsetti, S.S., Kolbe, J., Bieniek, E., Voswinckel, R. and Fink, L. (2012) Immune and Inflammatory Cell Involvement in the Pathology of Idiopathic Pulmonary Arterial Hypertension. *American Journal of Respiratory and Critical Care Medicine*, **186**, 897-908. https://doi.org/10.1164/rccm.201202-0335OC

[45] Chi, P.L., Cheng, C.C., Hung, C.C., Wang, M.T., Liu, H.Y. and Ke, M.W. (2022) MMP-10 from M1 Macrophages Promotes Pulmonary Vascular Remodeling and Pulmonary Arterial Hypertension. *International Journal of Biological Sciences*, **18**, 331-348. https://doi.org/10.7150/ijbs.66472

[46] Lepetit, H., Eddahibi, S., Fadel, E., Frisdal, E., Munaut, C. and Noel, A. (2005) Smooth Muscle Cell Matrix Metalloproteinases in Idiopathic Pulmonary Arterial Hypertension. *European Respiratory Journal*, **25**, 834-842. https://doi.org/10.1183/09031936.05.00072504

[47] Bendeck, M.P., Irvin, C. and Reidy, M.A. (1996) Inhibition of Matrix Metalloproteinase Activity Inhibits Smooth Muscle Cell Migration but Not Neointimal Thickening after Arterial Injury. *Circulation Research*, **78**, 38-43. https://doi.org/10.1161/01.RES.78.1.38

[48] Barman, S.A., Chen, F., Su, Y., Dimitropoulou, C., Wang, Y. and Catravas, J.D. (2014) NADPH Oxidase 4 Is Expressed in Pulmonary Artery Adventitia and Contributes to Hypertensive Vascular Remodeling. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **34**, 1704-1715. https://doi.org/10.1161/ATVBAHA.114.303848

[49] Wang, Z., Lakes, R.S., Eickhoff, J.C. and Chesler, N.C. (2013) Effects of Collagen Deposition on Passive and Active Mechanical Properties of Large Pulmonary Arteries in Hypoxic Pulmonary Hypertension. *Biomechanics and Modeling in Mechanobiology*, **12**, 1115-1125. https://doi.org/10.1007/s10237-012-0467-7

[50] Franz, M., Grun, K., Betge, S., Rohm, I., Ndongson-Dongmo, B. and Bauer, R. (2016) Lung Tissue Remodelling in MCT-Induced Pulmonary Hypertension: A Proposal for a Novel Scoring System and Changes in Extracellular Matrix and Fibrosis Associated Gene Expression. *Oncotarget*, **7**, 81241-81254. https://doi.org/10.18632/oncotarget.13220

[51] Ntokou, A., Dave, J.M., Kauffman, A.C., Sauler, M., Ryu, C., Hwa, J., *et al.* (2021) Macrophage-Derived PDGF-b Induces Muscularization in Murine and Human Pulmonary Hypertension. *JCI Insight*, **6**, e139067. https://doi.org/10.1172/jci.insight.139067

[52] Steiner, M.K., Syrkina, O.L., Kolliputi, N., Mark, E.J., Hales, C.A. and Waxman, A.B. (2009) Interleukin-6 Overexpression Induces Pulmonary Hypertension. *Circulation Research*, **104**, 236-244. https://doi.org/10.1161/CIRCRESAHA.108.182014

[53] D'Ignazio, L., Batie, M. and Rocha, S. (2017) Hypoxia and Inflammation in Cancer, Focus on HIF and NF-kB. *Biomedicines*, **5**, Article 21. https://doi.org/10.3390/biomedicines5020021

[54] Jin, F., Zheng, X., Yang, Y., Yao, G., Ye, L. and Doeppner, T.R. (2019) Impairment of Hypoxia-Induced Angiogenesis by LDL Involves a HIF-Centered Signaling Network Linking Inflammatory TNFα and Angiogenic VEGF. *Aging* (*Albany NY*), **11**, 328-349. https://doi.org/10.18632/aging.101726

[55] Canton, M., Sanchez-Rodrıguez, R., Spera, I., Venegas, F.C., Favia, M. and Viola, A. (2021) Reactive Oxygen Species in Macrophages: Sources and Target. *Frontiers in Immunology*, **12**, Article 734229. https://doi.org/10.3389/fimmu.2021.734229

[56] Khawaja, A.A., Chong, D.L.W., Sahota, J., Mikolasch, T.A., Pericleous, C. and Ripoll, V.M. (2020) Identification of a Novel HIF-1α-αMβ2 Integrin-NET Axis in Fibrotic Interstitial Lung Disease. *Frontiers in Immunology*, **11**, Article 2190. https://doi.org/10.3389/fimmu.2020.02190

[57] Walmsley, S.R., Print, C., Farahi, N., Peyssonnaux, C., Johnson, R.S. and Cramer, T. (2005) Hypoxia-Induced Neutrophil Survival Is Mediated by HIF-1α-Dependent NF-κB Activity. *Journal of Experimental Medicine*, **201**, 105-115. https://doi.org/10.1084/jem.20040624